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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,374	04/21/2005	Jay A Berzofsky	4239-67016-02	4276

36218 7590 06/08/2007

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EXAMINER	
HUFF, SHEELA JITENDRA	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
06/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,374	BERZOFSKY ET AL.	
	Examiner	Art Unit	
	Sheela J. Huff	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-18,21,25-28,32-34 and 38-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-18,21,25-28,32-34 and 38-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/15/06; 4/21/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 6-18, 21, 25-28, 32-34 and 38-45 are pending.

Information Disclosure Statement

The IDS filed on 3/15/06 and 4/21/05 have been considered and initialed copies of the PTO-1449 are enclosed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-12, 26-28 and 39-45 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. In claim the terminology "as colon tumor a uterine tumor" in line 2 renders the claim vague and indefinite. Is there supposed to be a comma between "tumor" and "a"?

b. In claims 11 and 12, there is no antecedent basis for "the agent".

c. In claim 26, it is not clear what activity of the immune cell is enhanced.

d. In claim 39, it is not clear of the TGF-beta cell in line 3 is the same or different from the control in lines 6 and 7. Additionally, it is not clear how the screening for a tumor inhibitor is accomplished using only TGF-beta receptor expressing cells and not tumor cells

Claims 39-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described in In Re Colianni, 195 USPQ 150 (CCPA 1977) and have been adopted by the Board of Patent Appeals and Interferences in Ex Parte Forman, 230 USPQ 546 (BPAI 1986). Among these factors are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the breath of the claims,
5. the amount of direction or guidance present, and
6. the presence or absence of working examples.

The following is an analysis of these factors in relationship to this application.

Applicant discloses and claims a screening method for agents that inhibit tumor recurrence comprising contacting a TGF-beta receptor expressing immune cell with TGF-beta or TGF-beta and agent wherein a decrease in activity in the cells treated with agent as compared to the control indicate that the agent can inhibit tumor recurrence.

The state of the art does not demonstrate that any such assay can be used to successfully result in an agent that can inhibit tumor recurrence. The state of the art

shows that TGF-beta and its receptors "are expression in essentially all tissues, and have been found to be important in many cellular processes since TGF-beta has been shown to play a role in cell growth and differentiation, immunosuppression, inflammation and the expression of extracellular matrix protein (see page 2 of specification, lines 5+). Thus TGF-beta is involved in a multitude of processes. Because TGF-beta is involved in so many distinct processes, one skilled in the art would not readily believe (absent any objective evidence) that an assay that shows decreased TGF-beta activity would necessarily result in an agent that inhibits tumor recurrence. The agent could be effective in inhibiting a different process such as inflammation.

Applicant's specification has not provided any examples of such a screening process nor has the monoclonal antibody used in the treatment aspect of the specification been used in the screening assay. One of skill in the art recognizes that extensive research must be done both in vitro and in vivo before a compound can be said to inhibit tumors. Applicant has not even provided any in vitro data. Even if applicant had provided in vitro data, one could not extrapolate this teaching to in vivo use because the *in vitro* experimental data would not be drawn to subjects with tumor cells. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant in vitro but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being

regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells in vivo are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Objections

Claim 12 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

This claim states that the agent results in lack of growth in vitro. However claim 1 only refers to in vivo use (due to the language of "administering" and "subject").

Double Patenting

Applicant is advised that should claim 1 be found allowable, claim 25 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6-9, 11-15, 21, 25-28, 32-34 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Dasch et al US 6090383.

This reference discloses and claims methods for treating tumor cells by administering monoclonal antibodies reactive to TGF-beta to suppress the immunosuppressive effects of TGF-beta and to permit generation of an immune response against the tumor and this results in tumor regression (col. 2, lines 28-32 and col. 5, lines 54-58). Tumors include sarcomas, melanomas and carcinomas (col. 2,

lines 8-10 and col. 5, lines 48-50). The preferred monoclonal antibody is Mab 1D11.16 (which is the same one used by applicant, col. 5, lines 18+). The antibody neutralizes the biological activity of TGF-beta an prevents binding of antigen to cell surface receptors (col. 5, lines 58-60). The biological activities of TGF-beta include affecting the proliferation and differentiation of cells of the immune system, such ash NK cells (col. 1, lines 20-40). The antibodies are can be administered by intraveneous or peritoneal perfusion or by bolus injection into the muscle or subcutaneous tissue (col. 6, lines 26-30) to patients (col. 6, lines 5-9).

With respect to claims 13-15, 27-28 and 33-34, since the monoclonal antibody used by applicant is the same as the monoclonal antibody used by the reference, the increased tumor immunosurveillance by lymphocytes and the lymphocyes surveyed are an intrinsic property of the monoclonal to effect the same cells in both the reference and the instant application.

With respect to tumor recurrence, applicant defines this as an inhibition (see page 17, lines 30-35 of the specification) and also defines treatment as tumor recurrence (see page 17, line 11 of the specification). Furthermore, the patent discloses the result being tumor regression which is what applicant is doing by the terminology "tumor recurrence". Thus, the patent reads on applicant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6-15, 21, 25-28, 32-34 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dasch et al US 6090383 in view of Suthanthiran et al US 2004-0197333 (filed 2/10/00).

Dasch et al has been discussed above.

The only difference between the instant invention and the reference is the specific mention of the difference types of cancers.

The secondary reference discloses the use of TGF-beta antagonists, which includes monoclonal antibodies (abstract, [0024]) to treat a variety of different cancers known to be associated with TGF-beta. These include cancers of the breast, lung, small intestine (reads on gastrointestinal), solon, kidney, ovary, prostate, brain, pancreas, skin, bone, uterus, testicles, cervix and liver ([0019).

Therefore, in view of the fact that is it known that TGF-beta antagonists, including monoclonal antibodies, to treat include cancers of the breast, lung, small intestine (reads on gastrointestinal), solon, kidney, ovary, prostate, brain, pancreas, skin, bone, uterus, testicles, cervix and liver and in view of the fact that mab 1D11.16 inhibits binding of TGF-beta to its receptor and inhibits its function (as disclosed in Dasch et al) (in other words 1D11.16 is behaving as an antagonist), it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to use 1D11.16 to treat cancers of the breast, lung, small intestine (reads on gastrointestinal), solon, kidney, ovary, prostate, brain, pancreas, skin, bone, uterus, testicles, cervix and liver.

Claims 1, 6-9, 11-18, 21, 25-28, 32-34 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dasch et al US 6090383 in view of Terabe et al Nature Immunology vol. 1 p. 515 (12/00).

Dasch et al has been discussed above. Dasch et al also disclose the use of the mab in an assay to monitor tumor mass (col. 6, lines 44-61). Thus, this reference is also disclosing methods for monitoring tumor progression (reads on tumor immunosurveillance).

The only difference between the instant invention and the reference is the specific mention of the specific assays used for tumor immunosurveillance.

The secondary reference shows that the assays of claims 16-18 are known in the art (see page 520, first column) and are used in tumor immunosurveillance (see entire reference).

Thus, in view of the known use of the assays for tumor immunosurveillance and in view of the fact that the primary reference calls for monitoring tumor progression, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to use these assays to monitor tumor progression.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Dasch et al J. Immunol. Vol. 142 p. 1536 (1989).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheela J. Huff whose telephone number is 571-272-0834. The examiner can normally be reached on Tuesday and Thursday from 5:30am to 1:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sheela J. Huff

Sheela J Huff
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sjh